283. The host cell of claim 282, wherein said polynucleotide is operably associated with a heterologous regulatory sequence.

284. A host cell comprising the polynucleotide of claim 273.

285. The host cell of claim 284, wherein said polynucleotide is operably associated with a heterologous regulatory sequence.

286. A method of producing a polypeptide comprising culturing the host cell of claim 282 under conditions such that said polypeptide is expressed, and recovering said polypeptide.--

Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 35-61, 79, 81-84, 86-100, 102-118, 120-153, 155-169, 176-189, 191-209, and 211-286 are pending in the application, with 35, 81, 96, 114, 132, 152, 169, 186, 205, 225, 242, 257, and 270 being the independent claims. The Examiner has allowed Claims 35, 39-46, and 49-57. Applicants note that the Examiner has acknowledged that the requirement for biological deposit for ATCC Deposit No. 97920 has been met with the submission of Statement Concerning the Deposited cDNA clone. *See* Paper No. 12 at page 3. Since the Examiner has not made any additional arguments which maintain the rejection of claims 132 and 139-147 in Paper No. 12, Applicants respectfully assert that these claims, as well, are in condition for allowance. The Examiner has withdrawn claims 60, 79, 150,

167, 203, and 223 from consideration due to a restriction requirement. Claims 19, 21, 62-78, 80, 85, 101, 119, 154, 170-175, 190, and 210 are sought to be canceled without prejudice to or disclaimer of the subject matter thereof. Applicants reserve the right to pursue the subject matter of these claims in related applications. New claims 225-286 are sought to be added. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Support for the Amendments

The claims have been amended for clarity, and to more particularly point out and distinctly claim the subject matter Applicants regard as the invention.

Support for the added claims may be found throughout the specification. Specifically, support for claims 225-228 and 270-272 may be found, *e.g.*, on page 4, lines 18-21, page 11, lines 15-18, in SEQ ID NO:1, and on page 26, line 23 through page 27, line 17. Support for added claims 229, 257, 258, and 273 may be found, *e.g.*, on page 8, lines 27-29, and in Example 6, page 53, line 20 to page 54, line 15. Support for added claim 259 may be found, *e.g.*, on page 17, lines 7-22 and in Example 5, page 51, line 30 through page 53, line 18. Support for added claims 232, 233, 249, 250, 262, 263, 277, and 278 may be found, *e.g.*, on page 13, lines 30-31, page 22, lines 19-33, and Example 6, page 53, line 20 to page 54, line 23. Support for added claims 242-246 may be found, *e.g.*, on page 29, line 28 through page 30, line 8, and on page 29, lines 5-8. Support for added claim 257 may be found, *e.g.*, on page 12, lines 19-33. Support for added claims 205-209 may be found, *e.g.*, on page 26, lines 18-27.

Accordingly, Applicants assert that the claims added herewith present no new matter.

The Restriction Requirement

The Examiner has stated the claims 60, 79, 150, 167, 203, and 223 embody subject matter which is distinct from the invention originally claimed. *See* Paper No. 12 at page 2.

Applicants respectfully traverse. Even assuming, *arguendo*, that claims 60, 79, 150, 167, 203, and 223 represent a distinct or independent invention, Applicants submit that to search and examine the subject matter of these claims together with the remainder of the pending claims would not be a serious burden on the Examiner. For example, publications which disclose host cells comprising TNF-family receptors normally also disclose that such host cells are useful to screen for ligand binding, thereby making it a simple matter for the Examiner to search and examine a method to screen for ligand binding utilizing host cells of the present invention. The M.P.E.P. § 803 (Seventh Edition, Rev. July, 1998) states:

> If the search and examination of an entire application can be made without serious burden, the examiner must examine it on the merits, even though it includes claims to independent or distinct inventions.

Thus, in view of the M.P.E.P. § 803, Applicants respectfully request that claims 60, 79, 150, 167, 203, and 223 be searched and examined in the subject application.

Applicants retain the right to petition from the restriction requirement under 37 C.F.R. § 1.144.

Inventorship

The inventors of the subject matter of the present application are Jian Ni, Reiner L. Gentz, Guo-Liang Yu, and Craig Rosen. Applicants have discovered that due to an inadvertent error Jeffery Su was originally named as an inventor in the present application, but should not have been so named. The M.P.E.P. § 201.03(E) provides that "[a]fter discovery of an inventorship error, the application can . . . be refiled under 37 C.F.R. § 1.53(d)(4) as a CPA where inventors are only to be deleted." Applicants note that under M.P.E.P. § 201.03(E), a newly executed oath or declaration is not necessary when inventors are only being deleted. Accordingly, upon the present refiling under 37 C.F.R. § 1.53(d)(4), Applicants respectfully request Jeffery Su be removed as an inventor.

Rejection under 35 U.S.C. § 112, Second Paragraph

(a) The Examiner has rejected claims 36, 37, 38, 47, 48, 58, 59, 61, 63, 64, 66, 67, 77, 78, 80, 82-85, 93-95, 97-99, 100, 101, 111-113, 115-119, 129-131, 133, 134, 137, 138, 148, 151, 207, 209-211, 221, 222, and 224 under 35 U.S.C.§ 112, second paragraph, alleging that the phrase "said nucleic acid" is indefinite, in that the independent claims refer to a nucleic acid and a "reference nucleic acid." *See* Paper No. 12 at page 3-4.

While not acquiescing to the Examiner's rejection, in order to expedite allowance of claims, Applicants have amended independent claims 35, 81, 96, 114, 132, and 205 to recite a "first" and a "second" nucleic acid, and have amended the corresponding dependent claims to refer

back to either the "first" or "second" nucleic acids so named. Accordingly, Applicants respectfully request that this aspect of the rejection be reconsidered, and further that it be withdrawn.

(b) The Examiner has rejected those claims referring to "a TNF ligand" *i.e.*, claims 47, 66, 85, 101, 119, 137 154, 190, and 210, under 35 U.S.C. § 112, second paragraph, stating that it is unclear what a TNF ligand is. *See* Paper No. 12 at page 4.

While not acquiescing to the Examiner's rejection, Applicants have canceled claims 66, 85, 101, 119, 154, 190, and 210, and have amended claims 47 and 137 to state that a polypeptide encoded by the claimed polynucleotide binds TRAIL. Similar language is used in added claims 229, 257, 258, and 273. Applicants reserve the right to pursue the canceled claims in related applications. Accordingly, Applicants respectfully request that this aspect of the rejection be reconsidered, and further that it be withdrawn.

(c) The Examiner has rejected claim 169 under 35 U.S.C. § 112, second paragraph, alleging that a polypeptide is not encoded by amino acids. *See* Paper No. 12 at page 4.

While not acquiescing to the Examiner's rejection, applications have amended line 4 of claim 169 to recite a polypeptide consisting of amino acids 1 to 360 of SEQ ID NO:2. Accordingly, Applicants respectfully request that this aspect of the rejection be reconsidered, and further that it be withdrawn.

In view of these remarks, Applicants respectfully request that the Examiner reconsider and withdraw all rejections under 35 U.S.C. § 112, second paragraph, as applied to the pending claims.

Rejections under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected "claims requiring the ability to encode a polypeptide that induces apoptosis or binds a TNF ligand and claims depending thereon . . . excluding claims 47, 48, and dependent claims, and claims 190, 191, and 204 as they related to polynucleotides with non-coding . . . strands" under 35 U.S.C. § 112, first paragraph, alleging that the specification does not provide enablement for polynucleotides encoding less than the full extracellular domain that bind a TNF ligand or less than the full-length or mature polypeptide which induces apoptosis. *See* Paper No. 12 at page 4. The Examiner further argues that the specification in not enabling for polynucleotides that comprise nucleic acids that are 90% identical to a nucleic acid encoding a specific set of amino acids of SEQ ID NO:2, which has the function of ligand binding or induction of apoptosis, stating that one of ordinary skill in the art could not reasonably predict which sequences besides those specifically disclosed would have the required functions. *See* Paper no. 12 at page 6.

Solely to advance prosecution, and not in acquiescence to the Examiner's rejection, Applicants have canceled claims 66, 67, 85, 101, 119, 154, 190, and 210, have amended claims 47 and 137, and have added claims 229, 257, 258, and 273 to specify that the claimed polynucleotide encode a polypeptide or polypeptide fragment which binds TRAIL, and have amended claim 191 and added claims 257-259 which specify that the polynucleotide hybridizes to the complementary strand. With respect to the pending claims, as amended, Applicants respectfully traverse.

Under the Federal Circuit standard for enablement, some necessary experimentation by the skilled artisan is permitted; the amount of experimentation, however, must not be unduly

extensive. *Atlas Powder Co. v. E. I. duPont de Nemours & Co.*, 750 F.2d 1569, 1577 (Fed. Cir. 1984). Furthermore, patent claims that include some claimed combinations which are inoperative are not necessarily invalid under 35 U.S.C. § 112. *Id.* As the Examiner has pointed out, factors to be considered when determining whether the amount of experimentation is undue were set out in *In re Wands*, 858 F.2d 731 at 737 (Fed. Cir. 1988). *See* Paper No. 12 at page 5.

The full extracellular domain of the DR5 polypeptide is described in the Specification to be amino acids 1 to 133 of SEQ ID NO:2. *See* the specification at page 11, lines 17-18. Accordingly, the full extracellular domain of the DR5 polypeptide is recited in added claim 225. Claim 137, as amended, refers to a polynucleotide encoding the mature DR5 polypeptide encoded by the cDNA clone in ATCC Deposit No 97920 which has the ability to bind TRAIL. Added claims 257 and 258 recite a polynucleotide comprising a nucleic acid which hybridizes to the complement of nucleotides 284-1362 of SEQ ID NO:1, wherein the nucleic acid encodes a polypeptide which binds TRAIL. The Examiner has stated that Example 6 provides enablement for the full DR5 extracellular domain binding TRAIL. *See* Paper No. 12 at page 5. Since each of claims 137, 225, 257, and 258 recite certain polynucleotides which encode the full DR5 extracellular domain, claims 137, 225, 257, and 258 each include specific embodiments which are enabled by disclosure of the present application.

Applicants further submit that claims 137, 225, 257, and 258 are enabled for their full scope using the rule set out in *Atlas Powder* and *Wands*. Given (a) the teachings of the present application, and (b) the high level of skill in the art regarding TNF-family receptor/ligand interactions, one of ordinary skill in the art could routinely make and use polynucleotides according to these claims which encode a polypeptide which binds TRAIL, without undue experimentation.

The specification teaches, at page 2, line 1 through page 4, line 2, and in the references cited therein, that a great deal is known about the ligand-binding domains of TNF-family receptors. For example, it is well known that specific conserved cysteine residues must be present for ligand binding to take place. Figure 2 shows a comparison of the amino acid sequences of four different TNF-family receptors, including DR5, which illustrates the conserved amino acids in the ligand binding extracellular domain important for TNF-family ligand binding activity. Furthermore, at the time of filing, the TNF-family ligand TRAIL had been isolated and characterized, and the genes for several receptors for TRAIL had been identified and sequenced. *See* the specification at page 3, line 22 through page 4, line 15, and the cited references therein. Accordingly, one of ordinary skill in the art could compare the deduced amino acid sequences of the ligand binding domains of the several receptors that bind TRAIL and thereby predict which conserved amino acids are required for TRAIL binding.

The specification further teaches: a method to screen for ligand binding (Example 6), conservative amino acid substitutions (pages 17, 18, and 25), and methods of mutagenesis to generate polypeptides with amino acid substitutions (page 25). Given the high level of skill in the art regarding the structure of TNF-family receptor ligand binding domains, and the teachings in the specification as to which amino acids must be conserved, methods to make conservative substitutions, and how to test for ligand binding, it would be a simple matter of routine experimentation for one of ordinary skill in the art to determine which polynucleotides actually encode a polypeptide capable of binding TRAIL. Since the skilled artisan has clear guidance as to which polynucleotides predictably will encode a polypeptide that will bind TRAIL, and only routine experimentation is required to screen for ligand binding, the possibility that some

polynucleotides embodied by the claims would not encode such a polypeptide does not defeat enablement.

Therefore, the specification is fully enabling for the polynucleotides recited in claims 137, 225, 257, and 258.

Added claim 273, recites an isolated polynucleotide comprising a nucleic acid which encodes a polypeptide fragment at least 90% identical to 50 contiguous amino acids of SEQ ID NO:2, wherein the polypeptide fragment is capable of functioning as part of a DR5 extracellular domain to bind TRAIL. One of ordinary skill in the art would readily understand from the specification and the art existing at the time of filing that a polypeptide comprising the claimed polypeptide fragment would have to include a ligand binding domain capable of binding TRAIL. For example, the claimed nucleic acid could encode a polypeptide related to a fragment of the protein consisting of amino acids 1 to 133 of SEQ ID NO:2, which binds TRAIL. As noted above in the remarks relating to claims 137, 225, 257, and 258, any additional structural features which might be required for TRAIL binding can be readily predicted based on the existing art and the disclosure provided in the present application, and only routine experimentation, the methods of which are disclosed, is required to determine whether a polypeptide encoded by a polynucleotide of the present invention actually binds TRAIL. Therefore, one of ordinary skill in the art could easily discern those polynucleotides encompassed by claim 273, which encode a polypeptide fragment capable of functioning as part of a DR5 extracellular domain to bind TRAIL. Since the skilled artisan has clear guidance as to which proteins comprising a claimed polypeptide fragment will bind TRAIL, and only routine experimentation is required to screen for ligand binding, the possibility that some polynucleotides embodied by the claims would not encode such a polypeptide fragment does not defeat enablement.

Claim 138 recites a polynucleotide comprising a first nucleic acid at least 90% identical to a second nucleic acid encoding the mature amino acid sequence encoded by the cDNA clone in ATCC Deposit No. 97920, wherein the first nucleic acid encodes a polypeptide which induces apoptosis. Added claims 257 and 259 recite polynucleotides comprising a nucleic acid which hybridizes to the complement of nucleotides 284-1362 of SEQ ID NO:1, wherein the polynucleotide encodes a polypeptide which induces apoptosis. The Examiner has stated that Example 5 provides enablement for the full-length receptor inducing apoptosis. *See* Paper No. 12 at page 5. Upon expression in eukaryotic cells, a full-length cDNA clone contained in ATCC Deposit No. 97920 would express the mature DR5 amino acid sequence on the surface of the cells. Similarly, certain polynucleotides which hybridize to the complement of nucleotides 284-1362 of SEQ ID NO:1 will encode a DR5 polypeptide. Since each of claims 138, 257, and 259 recite certain polynucleotides which encode the full-length DR5 polypeptide, claims 138, 257, and 259 each include specific embodiments which are enabled by disclosure of the present application.

Applicants further submit that claims 138, 257, and 259 are enabled for their full scope using the rule set out in *Atlas Powder* and *Wands*. Given (a) the teachings of the present application, and (b) the high level of skill in the art regarding TNF-family receptor death domains, one of ordinary skill in the art could routinely make and use the claimed polynucleotides which encode polypeptides which induce apoptosis, without undue experimentation.

The specification teaches, at page 2, line 22 to page 3, line 21, and in the references cited therein, that a great deal is known about the death domains of TNF-family receptors. Figure 2 shows a comparison of the amino acid sequences of four different TNF-family receptors, including DR5, which illustrates conserved amino acid regions throughout the respective polypeptides, including the death domain regions important for induction of apoptosis. Furthermore, at the time

of filing, the gene for DR4, another death domain containing receptor which binds TRAIL, had been identified and sequenced. *See* the specification at page 4, lines 3-6, and the references cited therein. Accordingly, one of ordinary skill in the art could compare the deduced amino acid sequences of the several TNF-family receptors which induce apoptosis, and in particular, the death domains, to predict which conserved amino acids are required for the induction of apoptosis.

The specification further teaches: a method to screen for apoptosis (Example 5), conservative amino acid substitutions (pages 17, 18, and 25), and methods of mutagenesis to generate polypeptides with amino acid substitutions (page 25). Given the high level of skill in the art regarding the structure of TNF-family receptor death domains, and the teachings in the specification as to: which amino acids should be conserved in the death domain and elsewhere in the polypeptide; methods to make conservative substitutions; and how to test for apoptosis; it would be a simple matter of routine experimentation for one of ordinary skill in the art to determine which polynucleotides encode polypeptides which induce apoptosis. Since the skilled artisan has clear guidance as to which polynucleotides will encode a polypeptide that will induce apoptosis, and only routine experimentation is required to screen for apoptosis, the possibility that some polynucleotides embodied by the claims would not encode such a polypeptide does not defeat enablement.

Therefore, the specification is fully enabling for the polynucleotides recited in claims 138, 257, and 259.

Claim 155, as amended, recites a polynucleotide comprising 30 contiguous nucleotides of nucleotides 754 to1362 of SEQ ID NO:1 encoding a polypeptide fragment which is capable of functioning as part of a mature DR5 polypeptide to induce apoptosis. Claims 100, 118, and 211, as amended, recite isolated polynucleotides comprising a first nucleic acid at least 90%

identical to a second nucleic acid encoding various polypeptide fragments of SEQ ID NO:2, wherein the first nucleic acid encodes a polypeptide fragment which is capable of functioning as part of a mature DR5 polypeptide to induce apoptosis. Claim 191, as amended, recites a polynucleotide comprising a nucleic acid which hybridizes to the complement of nucleotides 754-1362 of SEQ ID NO:1, wherein the nucleic acid encodes a polypeptide fragment which is capable of functioning as part of a mature DR5 polypeptide to induce apoptosis. Added claim 274 recites an isolated polynucleotide comprising a nucleic acid which encodes a polypeptide at least 90% identical to 50 contiguous amino acids within amino acids 1 to 360 of SEQ ID NO:2, wherein the nucleic acid encodes a polypeptide fragment which is capable of functioning as part of a mature DR5 polypeptide to induce apoptosis. One of ordinary skill in the art would readily understand from the specification and the art existing at the time of filing that a mature DR5 polypeptide comprising the claimed polypeptide fragment would have to include a death domain. For example, the nucleic acid could be (claim 155), or could be related to (claims 100, 118, 191, 211, and 274) a fragment of the polynucleotide comprising nucleotides 1099-1032 of SEQ ID NO:1, which encodes the DR5 death domain. As noted above in the remarks relating to claims 138, 257, and 259, additional structural features required for the induction of apoptosis in a mature DR5 polypeptide comprising the polypeptide fragment can be readily predicted based on the existing art and the disclosure provided in the present application. The specification further discloses the routine experimental methods to screen for apoptosis. Therefore, one of ordinary skill in the art could easily discern those polynucleotides encompassed by claims 100, 118, 155, 191, 210, and 274 which encode a polypeptide fragment which is capable of functioning as part of a mature DR5 polypeptide to induce apoptosis. Since the skilled artisan has clear guidance as to which polypeptides comprising the claimed polypeptide fragment will induce apoptosis, and only routine

experimentation is required to screen for apoptosis, the possibility that some polynucleotides embodied by the claims would not encode such a polypeptide does not defeat enablement.

In view of these remarks, Applicants respectfully request that the Examiner reconsider and withdraw all rejections under 35 U.S.C. § 112, first paragraph, as applied to the pending claims.

Rejections under 35 U.S.C. § 102

The Examiner has rejected claims 62, 63, 68, 69, 72-76, 152, 153, 156, 157-164, 169-173, 176, 177, 180-184, 186-189, 192, 193, 196-200, 205-209, 212, 213, and 216-219 under 35 U.S.C. 102(a) as being anticipated by GenBank Accession No. AA223122. *See* Paper No. 12 at page 7. The Examiner points out that GenBank Accession No. AA223122 is about 97% identical to nucleotides 236-698 of SEQ ID NO:1.

While not acquiescing to the Examiner's rejection, Applicants have canceled claims 62-78, 80, and 170-175, and have amended claims 152, 153, 169, 186, and 205. Applicants reserve the right to prosecute the canceled claims, as well as the subject matter subtracted from the amended claims, in related applications. Currently pending independent claims 152, 186, and 205, as amended, as well as their respective dependent claims, comprise at least 30 contiguous nucleotides or, or hybridize to nucleotides 754 to 1362 of SEQ ID NO:1, or comprise a nucleic acid at least 90% identical to a nucleic acid encoding 30 contiguous amino acids from 158-360 of SEQ ID NO:2. Furthermore, the polynucleotides encoding epitopes of claims 169 and 242, and the polynucleotides encoding polypeptides of claims 225, 257, and 270 all require that the polynucleotide encode a polypeptide which cannot be encoded by GenBank Accession No.

AA223122. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 102(a) over GenBank Accession No. AA223122.

Based on these remarks, Applicants respectfully request that the rejection under 35 U.S.C. § 102(a), as applied to the pending claims, be withdrawn.

Rejection under 35 U.S.C. § 103

The Examiner has rejected claims 62, 63, 68, 69, 72-76, 152, 153, 156, 157-164, 169-173, 176, 177, 180-184, 186-189, 192, 193, 196-200, 205-209, 212, 213, and 216-219, as well as claims 70-71, 158-159, 178-179, 185, 194-195, and 214-215 under 35 U.S.C. § 103(a) as being unpatentable over GenBank Accession No. AA223122 and Chinnaiyan, *et al.*, *Science 274*:990-992 (1996), Sibson, *et al.*, WO 94/01548, and Bjorn *et al.*, *Current Biol. 2*:569-575 (1992), in view of Adair *et al.*, WO 91/09967. The Examiner asserts that Chinnaiyan *et al.* teaches expression of a DR3-encoding polynucleotide, WO 94/01548 teaches the desirability of expressing ESTs, Bjorn *et al.* teach Ig-Fc fusion proteins, and Adair teaches that non-human antibodies are antigenic in humans, and that these references, in combination with the EST disclosed as GenBank Accession No. AA223122, renders the above-mentioned claims obvious.

Applicants have asserted, *supra*, that the pending claims are novel and non-obvious over GenBank Accession Number AA223122. The remaining references cited by the Examiner do not establish a *prima facie* case of obviousness, because there is no teaching of a polynucleotide comprising a nucleic acid, or a fragment thereof, which is recited in the pending claims. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) over the three references cited by the Examiner, be withdrawn.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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